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ORIGINAL RESEARCH

The EVA (Early Vascular Aging) Study: Association of Central Obesity With Worse Arterial Health After Preeclampsia

Amélie Paquin, MD, MSc; Ana Werlang, MD; Thais Coutinho, MD

BACKGROUND: Women with preeclampsia have a higher risk of cardiovascular disease. This is partly explained by the worse arterial health after preeclampsia. Central obesity (CO) is a risk factor for both preeclampsia and cardiovascular disease. Whether CO contributes to further worsening of arterial health after preeclampsia remains unclear. Our objective was to evaluate the effect of CO and previous preeclampsia on arterial hemodynamics.

METHODS AND RESULTS: We studied 40 women with previous preeclampsia (<6 years) and 40 age-matched controls with previous normotensive pregnancy in the same timeframe. We estimated arterial hemodynamics with validated techniques combining applanation tonometry and echocardiography. CO was defined as a waist-to-hip ratio ≥0.85. Differences in arterial hemodynamics across the 3 groups (preeclampsia with CO, preeclampsia without CO, and controls) were assessed with multivariable linear regression models adjusted for potential confounders. Twenty-six (65%) of the participants with preeclampsia had CO compared with 18 (45%) controls. Mean waist-to-hip ratio in patients with preeclampsia with CO, those with preeclampsia and no CO, and controls was 0.94±0.05, 0.80±0.04, and 0.83±0.07, respectively. In multivariable analyses, women with preeclampsia and CO had higher central blood pressure, arterial stiffness (carotid-femoral pulse wave velocity), steady arterial load (systemic vascular resistance), and wave reflections (reflected pressure wave amplitude, augmentation index) compared with controls (P<0.05 for each). Fewer hemodynamic domains were altered in the preeclampsia with no CO group, with higher central diastolic blood pressure, systemic vascular resistance, and wave reflections than controls (P<0.05).

CONCLUSIONS: Women with previous preeclampsia who also experience CO have the greatest alterations in arterial health and hemodynamics. Patients with preeclampsia with CO may represent a higher-risk subgroup who could be targeted for risk stratification and primary prevention of cardiovascular disease.

Key Words: arterial hemodynamics ■ arterial stiffness ■ central obesity ■ preeclampsia

Cardiovascular disease (CVD) risk factors differ significantly between men and women. Although cardiometabolic disorders are more prevalent among men, their effect on cardiovascular prognosis appears worse in women.[1] Moreover, women are affected by conditions that impact their cardiovascular risk and are specific to their sex. For instance, hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, and eclampsia, increase their lifetime risk of developing hypertension and heart failure 4-fold and more than double their risk of coronary heart disease and cardiovascular mortality.[2] Preeclampsia is prevalent and affects ≈5% to 10% of pregnancies.[3] Despite the increased overall risk, most women with history of preeclampsia do not develop CVD,[4] and therefore systematically implementing lifelong risk stratification and preventative strategies for all women who develop preeclampsia each year is not feasible at the health care system level. As such, there is a critical need to better understand and target

Correspondence to: Thais Coutinho, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. Email: coutinho.thais@mayo.edu

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CLINICAL PERSPECTIVE

What Is New?

- The EVA (Early Vascular Aging) study is the first to describe the contribution of central obesity in adversely affecting arterial health and central hemodynamics in women with previous preeclampsia.
- Because aortic stiffness and other parameters of arterial hemodynamics have been independently associated with adverse cardiovascular prognosis, our results suggest that women affected by both a history of preeclampsia and central obesity may be more likely to face a higher risk of future cardiovascular events.

What Are the Clinical Implications?

- Women with a history of preeclampsia who are affected by central obesity display significant abnormalities in arterial health and may represent a higher cardiovascular risk subgroup deserving of enhanced risk stratification and preventative strategies.
- Deteriorations in arterial health and aging can be prevented or decelerated by lifestyle interventions with nutritional and exercise components.
- Such strategies could be considered for evaluation and implementation of primary cardiovascular prevention programs targeting women with central obesity and a history of preeclampsia.

Nonstandard Abbreviations and Acronyms

AIx	augmentation index
cfPWV	carotid-femoral pulse wave velocity
CO	central obesity
CTL-CO	controls with central obesity
CTL-noCO	controls without central obesity
GRC	global reflection coefficient
PAC	proximal aortic compliance
P_b	reflected pressure wave amplitude
PE-CO	preeclampsia with central obesity
PE-noCO	preeclampsia without central obesity
P_f	forward pressure wave amplitude
TAC	total arterial compliance
WHR	waist-to-hip ratio

cardiovascular risk in this population, helping us identify the individuals who are most likely to benefit from cardiovascular risk assessment and preventative strategies.

Traditional cardiovascular risk factors also increase the risk of developing preeclampsia. Major risk factors include obesity (relative risk, 2.8; as compared with women who have normal body mass index), chronic hypertension (relative risk, 5.1), and diabetes (relative risk, 3.7).[5] Yet, an analysis of the Nurses' Health Study II revealed that the prevalence of traditional and cardiometabolic risk factors accounts for only 57% of the relationship between preeclampsia and CVD,[4] suggesting that preeclampsia may affect other aspects of cardiovascular health not directly inferred by the presence of conventional risk factors. In this context, preeclampsia has been linked to abnormal arterial health and early vascular aging.[6] Early vascular aging is commonly defined as arterial stiffness (often quantified by the carotid-femoral pulse wave velocity, cfPWV) higher than age-specific normal values established in the general population.[7] In a study by Bruno et al, an estimated vascular age of >5.7 years higher than chronological age was associated with at least twice the risk of cardiovascular events at 6-year follow-up.[8] As such, parameters of arterial health and aging represent significant and independent risk factors for CVD.[9,10] Using arterial hemodynamics as early subclinical tools to evaluate cardiovascular health and risk, we designed the EVA (Early Vascular Aging) study to identify subgroups of women with previous preeclampsia who display the greatest abnormalities in arterial hemodynamics and who would therefore most likely benefit from risk stratification and management strategies.[6]

Obesity is a common risk factor for both preeclampsia and CVD.[3,11] Obesity, more specifically central obesity (CO), which reflects visceral adiposity, contributes to the development of CVD via increased insulin resistance, oxidative stress, endothelial dysfunction, and production of inflammatory cytokines.[11] Similar to preeclampsia, CO has also been associated with altered arterial health and worse arterial stiffness.[12] However, it is unclear whether the combination of preeclampsia and CO further affects arterial hemodynamics and accelerates arterial aging. Thus, we hypothesized that women affected both by CO and a previous preeclamptic pregnancy would present with worse arterial health in the EVA study.

METHODS

The EVA study was a cross-sectional study that included 40 women with previous preeclampsia, as defined by the American College of Obstetricians and Gynecologists,[13] and 40 age-matched controls with previous normotensive pregnancy(ies). Participants were 18 years and older and were 6 months to 6 years postpartum. This time frame was selected specifically to avoid studying participants too early and therefore still have hemodynamic influences from pregnancy, while at the same time avoiding studying them so late

postpartum that overt CVD would already have developed (the average time frame between preeclampsia and first cardiovascular event among affected individuals is 10 years).[14] Participants were identified and recruited between 2017 and 2021, via a keyword search in the electronic medical records from The Ottawa Hospital Labor and Delivery of preeclamptic or normotensive pregnancies in the past 5 years. Participants could also be referred by their treating physician to the research study. Exclusion criteria were previous surgical aortic repair or aortic valve replacement, more than mild aortic stenosis, more than moderate aortic regurgitation, or permanent atrial fibrillation/flutter. During the study visit, participants completed a standardized questionnaire regarding their self-identified race or ethnicity (optional) and past medical, gynecological, and obstetrical histories and medication use. The study visit also included anthropometric measurements and a blood sample for measurement of fasting lipids, glycated hemoglobin, and creatinine. CO was defined as a waist-to-hip ratio (WHR) ≥0.85 according to World Health Organization criteria for women.[15] Hypertension was defined as a clinical diagnosis established by a physician or use of antihypertensive medication. Diabetes was defined as a clinical diagnosis established by a physician or use of insulin or hypoglycemic medication. Smoking history was defined as having smoked at least 100 cigarettes in their lifetime. This project was approved by the University of Ottawa Heart Institute's research ethics board. All participants provided written and informed consent.

Noninvasive Assessment of Arterial Hemodynamics

Arterial hemodynamics were evaluated with previously validated methods that combine arterial waves from peripheral arterial tonometry and volume/flow quantification echocardiography (NIHem, Cardiovascular Engineering) to comprehensively estimate five domains of arterial hemodynamics: (1) arterial stiffness determined by the cfPWV; (2) central systolic, diastolic, and pulse pressures; (3) pulsatile arterial load: forward pressure wave amplitude (P_f; forward portion of the arterial wave generated by the interaction of systolic ejection pressure and the proximal aorta), aortic characteristic impedance (opposition of the aorta to pulsatile flow in early systole), proximal aortic compliance (PAC), total arterial compliance (TAC; compliance of the whole arterial system); (4) steady arterial load determined by the systemic vascular resistance (SVR); (5) peripheral wave reflections: reflected pressure wave amplitude (P_b; portion of the arterial wave that is reflected back to the proximal aorta at sites of impedance mismatch), augmentation index (AIx; ratio of augmented pressure to central pulse pressure), global reflection coefficient (GRC; ratio of P_b divided by P_f).[16,17] Further details of the arterial hemodynamic assessment have been previously described by our group and are presented in Data S1.[6,18–20]

Statistical Analysis

Participants were categorized into 3 groups based on history of previous preeclampsia and on WHR: (1) previous preeclampsia with CO (PE-CO); (2) previous preeclampsia without CO (PE-noCO); and (3) controls. We performed descriptive analysis of all 3 groups. Continuous data are presented as mean±SD if normally distributed, or as median and range if nonnormally distributed. Groups were compared using 1-way ANOVA or Mann–Whitney Wilcoxon test according to the normality of distribution for continuous variables. Categorical variables were compared between groups with χ^2 or Fisher exact test, as appropriate. Pairwise hemodynamic comparisons between the 3 groups were performed using a *t*, Wilcoxon, χ^2, or Fisher exact test, accordingly. The association of CO and preeclampsia with parameters of arterial hemodynamics was evaluated with multivariable regression models, adjusting for covariables previously described as associated with arterial hemodynamics: age, hypertension, diabetes, serum creatinine, tobacco smoking, gravidity, time since last pregnancy, and heart rate.[16,21–25] The covariables were sequentially added to the models to determine which model represented the highest proportion of variance in prediction of cfPWV (the gold-standard measure of aortic stiffness and arterial aging) according to the adjusted R^2 value and to the Akaike information criterion. The model with the highest adjusted R^2 and lowest Akaike information criterion was used to assess the other arterial hemodynamic parameters. In sensitivity analyses to confirm our variable selection, we also performed combined stepwise linear regression models with criteria of $P \leq 0.25$ to enter and $P \leq 0.10$ to stay in the model (variables considered included age, hypertension, diabetes, history of smoking, serum creatinine, heart rate, gravidity, time since last pregnancy, and the PE-CO groups). Data were considered to be missing at random, and participants with missing hemodynamic data were excluded from analyses that evaluated the hemodynamic measure that was missing. Last, in sensitivity analyses to further evaluate the combined effect of PE-CO on arterial health, we repeated the multivariable regression models separating controls with CO (CTL-CO) and controls without CO (CTL-noCO). Results of the multivariable linear regression models are presented as adjusted mean differences and their 95% CI. A 2-sided *P* value <0.05 was considered statistically significant. Software JMP version 16 (SAS Institute Inc) was used. The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Description of Participants

Among participants with previous preeclampsia, 26 (65%) had a WHR ≥0.85 and were included in the PE-CO group. In the control group, 18 (45%) women met criteria for CO (Figure 1). Characteristics of the participants are presented in Table 1. Mean age and median gravidity were similar among all 3 study groups. The time since last pregnancy was approximately 6 months longer in the preeclampsia groups compared with the controls (1.8 years [0.5–4.4 years] versus 2.5 years [0.8–5.7 years], respectively; P=0.03). Six (23%) and 3 (21%) participants, respectively, in the PE-CO and PE-noCO groups had recurrent preeclampsia before their index pregnancy (P=0.91). Three participants (12%) had a diagnosis of diabetes, 4 (15%) had a diagnosis of gestational diabetes, and 7 (27%) had a diagnosis of hypertension in the PE-CO group. Glycated hemoglobin was significantly higher in the PE-CO group compared with the other 2 groups (P=0.007). Serum triglyceride, low-density lipoprotein cholesterol, and non–high-density lipoprotein cholesterol levels were higher and high-density lipoprotein cholesterol levels were lower in the PE-CO group compared with controls (P<0.05 for each).

Measures of Arterial Hemodynamics

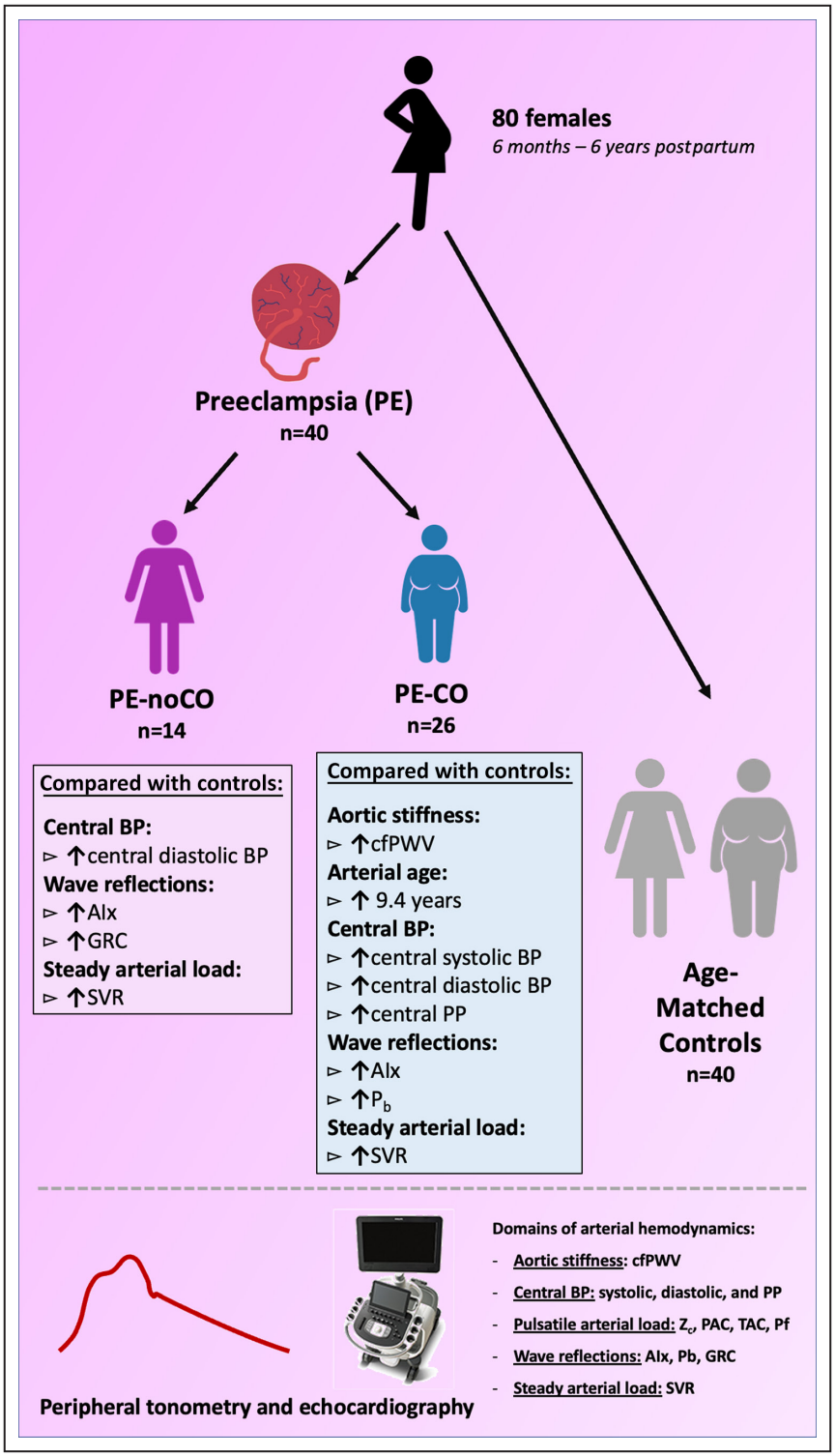
Measures of arterial hemodynamics per study group are presented in Table 2. cfPWV and PAC were missing in 1 participant (control), and SVR, aortic characteristic impedance, PAC, TAC, P_f, and P_b were missing in 1 participant (PE-noCO) due to technical issues. Participants in the PE-CO group exhibited higher brachial and central blood pressures (BPs), aortic stiffness (cfPWV), steady arterial load (SVR), pulsatile arterial load (higher P_f and lower PAC and TAC), and wave reflections (AIx) as compared with controls. Conversely, hemodynamic alterations were less prominent in the participants with PE-noCO, who only exhibited higher steady arterial load (SVR) and wave reflections (AIx and GRC) than controls. Compared with women with PE-noCO, women with PE-CO had higher central systolic BP, pulsatile arterial load (lower PAC and TAC and higher P_f), and more wave reflections (higher GRC).

Multivariable linear regression models assessing the association of PE-CO with cfPWV adjusting for different combinations of covariables are presented in Table 3. The adjusted mean differences in cfPWV among the 5 models were consistent, with the highest adjusted R^2 value and lowest Akaike information criterion observed in models that included age, hypertension, diabetes, smoking history, serum creatinine, and heart rate (model 5). In the stepwise model, the following variables met criteria to be included in the final model: age, hypertension, diabetes, history of smoking, serum creatinine, heart rate, and the PE-CO groups. However, this model had lower R^2 values (0.356) and higher Akaike information criterion (194.93) than model 5. Thus, linear regression models for the remaining hemodynamic parameters were performed adjusting for the same set of variables as in model 5. Results are presented in Table 4 and in Figures 1 and 2. After adjustment for potential confounders, women in the PE-CO group had higher central systolic, diastolic, and pulse pressure, as well as higher cfPWV, SVR, P_b, and AIx (P<0.05 for each). Mirroring the findings from unadjusted analyses, women with PE-noCO had higher brachial and central diastolic BP, SVR, AIx, and GRC than controls (P<0.05 for each). Significant differences between the preeclampsia groups included higher central systolic BP and central pulse pressure and lower GRC for PE-CO compared with PE-noCO (P<0.05 for each). No statistically significant differences were found among groups regarding aortic characteristic impedance, PAC, TAC, and $P_{f,}$ after adjustment for confounders.

In sensitivity analyses, when separating controls with (n=22) and without (n=18) CO, women in the PE-CO group had higher central systolic and diastolic pressure, as well as higher cfPWV and AIx when compared with both CLT-CO and CTL-noCO women (P<0.05 for each; Table S1). SVR and PAC were also higher in the PE-CO group compared with the CTL-noCO group. Women with PE-noCO had higher AIx and GRC than CTL-CO women and higher central diastolic pressure, AIx, and GRC than CTL-noCO (P<0.05 for each).

To enhance interpretation and clinical translatability of our results, we compared the differences in cfPWV between women with PE-CO and controls against published normative values for cfPWV in people in their 30s,

Figure 1. Summary of the study protocol and main result findings.
Twenty-six women with previous PE-CO were compared with 14 women with previous PE-noCO, 18 women with previous normotensive pregnancies and central obesity, and 22 women with previous normotensive pregnancies and no central obesity. Extensive evaluation of arterial health parameters was performed in all participants with the combination of echocardiography and applanation tonometry. The 4 study groups were compared with multivariable linear regression models adjusting for age, time since last pregnancy, hypertension, creatinine, smoking history, and heart rate. Significant differences between groups (P<0.05) are shown in the figure. AIx indicates augmentation index; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; GRC, global reflection coefficient; PAC, proximal aortic compliance; P_b, reflected pressure wave amplitude; PE-CO, preeclampsia with central obesity; PE-noCO, preeclampsia without central obesity; P_f, forward wave amplitude; PP, pulse pressure; TAC, total arterial compliance; SVR, systemic vascular resistance; and Z_c, aortic characteristic impedance.



which is similar to the mean age of our participants.[26] Such normative values indicate a cfPWV increase of 0.7 m/s per decade in this age group. In our study, the adjusted mean difference in cfPWV between women with PE-CO and controls was 0.66 m/s, corresponding to an additional 9.4 years of vascular age for women with a previous history of preeclampsia who have CO.

DISCUSSION

From the EVA study, our results demonstrate that women with previous PE-CO have worse central BP, arterial stiffness, and peripheral wave reflections independently from confounders, as compared with controls without preeclampsia, with and without CO. With

Table 1. Description of Participant Characteristics

Characteristics	PE-CO (n=26)	PE-noCO (n=14)	CTL-CO (n=18)	CTL-noCO (n=22)	*P* value
Age, y	36.2±4.6	34.6±4.4	34.6±2.5	36.8±3.3	0.19
Race or ethnicity, n (%)					0.60
White	17 (81)	13 (100)	16 (84)	14 (100)	
Black	0 (0)	0 (0)	1 (5)	0 (0)	
Hispanic	1 (5)	0 (0)	2 (11)	0 (0)	
Filipino	2 (10)	0 (0)	0 (0)	0 (0)	
Other	1 (5)	0 (0)	0 (0)	0 (0)	
BMI, m^2/kg	32.0 (21.2–59.5)*†§	24.3 (19.7–40.2)*	26.3 (20.3–35.9)†	23.2 (19.3–35.4)§	0.001
WHR	0.94 (0.86–1.03)*†§	0.81 (0.72–0.85)*‡	0.88 (0.86–0.95)†‡	0.79 (0.70–0.85)§	<0.0001
Gravidity, n (range)	2 (1–7)	2 (1–6)	2 (1–4)	2 (1–5)	0.56
Time since last pregnancy, y	1.9 (0.6–4.7)	1.9 (0.5–3.8)	2.0 (0.8–5.7)†	2.5 (1.0–4.1)	0.18
Recurrent preeclampsia, n (%)	6 (23)	3 (21)	…	…	0.91
Diabetes, n (%)	3 (12)§	0 (0)	0 (0)	0 (0)§	0.07
Gestational diabetes, n (%)	4 (15)	0 (0)	0 (0)	0 (0)	0.048
Dyslipidemia, n (%)	1 (4)	2 (14)	1 (6)	0 (0)	0.25
Hypertension, n (%)	7 (27)†§	1 (7)	0 (0)†	0 (0)§	0.002
Smoking history, n (%)	9 (35)	4 (29)	5 (28)	4 (18)	0.64
Diuretics, n (%)	1 (4)	0 (0)	0 (0)	0 (0)	1.00
β-Blockers, n (%)	1 (4)	0 (0)	0 (0)	0 (0)	1.00
Calcium channel blockers, n (%)	4 (15)	0 (0)	0 (0)	0 (0)	0.048
ACEI, n (%)	2 (8)	0 (0)	0 (0)	0 (0)	0.43
Creatinine, mg/dL	0.68 (0.52–0.93)	0.70 (0.53–0.86)	0.68 (0.53–0.89)	0.72 (0.58–0.87)	0.69
Glycated hemoglobin, %	5.35 (4.8–6.2)*†	5.15 (4.8–5.5)*	5.05 (4.4–5.8)†	5.15 (4.4–5.7)	0.02
Total cholesterol, mg/dL	182 (143–309)	184 (120–228)	172 (131–263)	170 (112–240)	0.23
LDL cholesterol, mg/dL	106 (77–189)§	104 (46–128)	101 (54–174)	87 (43–151)§	0.02
Non–HDL cholesterol, mg/dL	128 (85–263)§	118 (70–155)	114 (62–193)	104 (62–174)§	0.01
HDL cholesterol, mg/dL	54 (32–89)*†§	70 (41–96)*	62 (43–81)†	64 (50–103)§	0.02
Triglycerides, mg/dL	100 (50–371)*†§	62 (35–238)*	72 (41–178)†	73 (33–337)§	0.01

Values are presented as number (proportion), mean±SD, or median (range). ACEI indicates angiotensin-converting enzyme inhibitor; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and WHR, waist-to-hip ratio.

*P value <0.05 for pairwise comparison between preeclampsia with central obesity (PE-CO) and preeclampsia without central obesity (PE-noCO).

†P value <0.05 for pairwise comparison between PE-CO and controls with central obesity (CTL-CO).

‡P value <0.05 for pairwise comparison between PE-noCO and CTL-CO.

§P value <0.05 for pairwise comparison between PE-CO and controls without central obesity (CTL-noCO).

early vascular aging being defined as vascular age greater than chronological age by >5.7 years, women with PE-CO exhibited a significant degree of early vascular aging, with an average additional 9 years of vascular age compared with normative values.[8,26] They also exhibited worse arterial compliance than controls with CO and women with PE-CO, but this association was not independent of confounders. Further, women with previous PE-noCO had similar arterial hemodynamics compared with controls, with the exception of higher GRC among the former.

The EVA study is the largest to pursue noninvasive and extensive assessment of arterial hemodynamics in its multiple domains among women with previous preeclampsia. In the EVA study, we previously demonstrated that preeclampsia affected all of these domains in the intermediate postpartum term, with obstetrical factors such as preeclampsia severity, timing, and recurrence significantly and negatively affecting arterial health.[6] The present study's findings are novel and further build on our line of work by demonstrating maternal factors (CO) that contribute to worse arterial hemodynamic profile among women with a history of preeclampsia. This is clinically relevant, because these measures of arterial hemodynamics, including early vascular aging, have been recognized as independent predictors of CVD events in large populational cohort studies.[8,10,27–29] We observed a higher GRC among PE-noCO women compared with women with PE-CO. GRC assesses wave reflection intensity and is calculated by the ratio of P_b/P_f.[30] This result is thus explained by the observation of higher P_f without a proportional

Table 2. Measures of Arterial Hemodynamics by Study Group

Hemodynamic measurements	PE-CO (n=26)	PE-noCO (n=14)	CTL-CO (n=18)	CTL-noCO (n=22)	*P* value
Brachial BP					
Systolic BP, mm Hg	114 (95–160)*†§	106 (90–126)	105 (88–118)†	100 (87–122)§	0.0003
Diastolic BP, mm Hg	65 (52–103)*†§	59.5 (49–80)*	55 (44–65)†	53 (43–67)§	<0.0001
Mean arterial BP, mm Hg	86 (73–130)*†§	80 (62–95)*	73 (61–83)†	72 (58–91)§	<0.0001
Brachial PP, mm Hg	51 (32–84)	46 (37–64)	47 (31–71)	46 (31–56)	0.57
Central BP					
Central systolic BP, mm Hg	116 (89–163)*†§	103 (77–117)*	96 (80–111)†	92 (71–114)§	<0.0001
Central diastolic BP, mm Hg	65 (52–103)†§	60 (49–80)	55 (44–65)†	53 (43–67)§	<0.0001
Central PP, mm Hg	51 (28–86)§	39 (23–56)	39 (28–64)	39 (24–50)§	0.03
Aortic stiffness					
cfPWV, m/s	6.74 (4.69–8.23)†§	5.98 (3.96–7.22)	5.44 (5.00–7.42)†	5.54 (3.60–7.25)§	0.003
Steady arterial load					
SVR, dyne×s/cm^5	1853 (1421–3405)†§	1938 (1241–2458)	1620 (1190–2277)†	1518 (1145–2218)§	0.0007
Pulsatile arterial load					
Z_c, dyne×s/m^5	197 (91–343)§	166 (96–262)	184 (98–281)	163 (107–255)§	0.08
PAC, ×10^{-6}cm^4/dyne	8.54 (3.57–19.20)*†§	10.40 (7.45–18.44)*	9.45 (7.19–18.74)†	10.42 (7.34–23.75)§	0.005
TAC, mL/mm Hg	1.22 (0.81–2.23)*†§	1.67 (0.76–2.54)*	1.53 (1.05–2.92)†	1.72 (1.07–3.08)§	0.02
P_f, mm Hg	44.3 (24.5–66.2)*	32.2 (18.7–45.4)*	37.2 (25.1–64.6)	36.9 (21.5–50.3)	0.06
Peripheral wave reflections					
P_b, mm Hg	13.35 (7–30.2)	12.5 (8.2–17.9)	10.75 (8.6–15.8)	11.05 (7.7–18.6)	0.19
AIx, %	8.5 (–18.2 to 28.7)†§	14.3 (5–21.3)	1.15 (–13.3 to 15.3)†	–1.05 (–13.7 to 17.5)§	0.0002
Global reflection coefficient	0. 32 (0.17–0.46)*	0.38 (0.32–0.46)*	0.30 (0.23–0.37)	0.34 (0.20– 0.48)	0.003

AIx indicates augmentation index; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; PAC, proximal aortic compliance; P_b, reflected pressure wave amplitude; P_f, forward pressure wave amplitude; PP, pulse pressure; SVR, systemic vascular resistance; TAC, total arterial compliance; and Z_c, aortic characteristic impedance.

*P value<0.05 for pairwise comparison between preeclampsia with central obesity (PE-CO) and preeclampsia without central obesity (PE-noCO).

†P value<0.05 for pairwise comparison between PE-CO and controls with central obesity (CTL-CO).

‡P value<0.05 for pairwise comparison between PE-noCO and CTL-CO.

§P value<0.05 for pairwise comparison between PE-CO and controls without central obesity (CTL-noCO).

Table 3. Summary of Progressively Adjusted Multivariable Linear Regression Models of the Association of Previous PE-CO With cfPWV

Study group	Model 1* aMD [95% CI] (m/s) *P* value	Model 2† aMD [95% CI] (m/s) *P* value	Model 3‡ aMD [95% CI] (m/s) *P* value	Model 4§ aMD [95% CI] (m/s) *P* value	Model 5‖ aMD [95% CI] (m/s) *P* value
CTL-noCO	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
CTL-CO	0.13 [–0.43 to 0.68] *P*=0.65	–0.02 [–0.78 to 0.74] *P*=0.96	0.09 [–0.45 to 0.63] *P*=0.75	0.09 [–0.68 to 0.86] *P*=0.82	0.16 [–0.57 to 0.90] *P*=0.66
PE-noCO	0.40 [–0.18 to 0.99] *P*=0.17	0.66 [–0.07 to 1.38] *P*=0.08	0.29 [–0.28 to 0.87] *P*=0.31	0.59 [–0.14 to 1.31] *P*=0.11	0.56 [–0.15 to 1.27] *P*=0.12
PE-CO	0.92 [0.43–1.41] *P*=0.0003	1.15 [0.52–1.78] *P*=0.0006	0.74 [0.22–1.27] *P*=0.006	0.99 [0.32–1.66] *P*=0.005	0.91 [0.26–1.56] *P*=0.007
R^2	0.218	0.277	0.273	0.308	0.362
AIC	205.24	164.74	205.16	167.31	160.57

AIC indicates Akaike information criterion; aMD, adjusted mean difference; CTL-CO, controls with central obesity; CTL-noCO, controls without central obesity; cfPWV, carotid-femoral pulse wave velocity; PE-CO, preeclampsia with central obesity; and PE-noCO, preeclampsia without central obesity.

*Model 1: adjusted for age.

†Model 2: adjusted for age, gravidity, and time since last pregnancy.

‡Model 3: adjusted for age, hypertension, diabetes, serum creatinine, and smoking history.

§Model 4: adjusted for age, hypertension, serum creatinine, smoking history, gravidity, and time since last pregnancy.

‖Model 5: adjusted for age, time since last pregnancy, hypertension, serum creatinine, smoking history, and heart rate.

Table 4. Multivariable Linear Regression Analysis of the Association of Previous PE-CO With Measures of Arterial Hemodynamics

Hemodynamic measures	Controls as reference		PE-noCO group as reference
	aMD [95% CI] PE-CO vs controls *P* value	aMD [95% CI] PE-noCO vs controls *P* value	aMD [95%CI] PE-CO vs PE-noCO *P* value
Brachial BP			
Systolic BP, mm Hg	11 [5–19] *P*=0.001	6 [–2 to 14] *P*=0.14	6 [–3 to 15] *P*=0.20
Diastolic BP, mm Hg	11 [6–15] *P*<0.0001	7 [1–12] *P*=0.02	4 [–2 to 10] *P*=0.18
Mean arterial BP, mm Hg	13 [7–18] *P*<0.0001	6 [0–12] *P*=0.048	6 [0–13] *P*=0.07
Brachial PP, mm Hg	1 [–4 to 7] *P*=0.67	–1 [–7 to 6] *P*=0.87	2 [–6 to 9] *P*=0.64
Central BP			
Central systolic BP, mm Hg	17 [9–25] *P*<0.0001	5 [–4 to 14] *P*=0.26	12 [2–22] *P*=0.02
Central diastolic BP, mm Hg	11 [6–15] *P*<0.0001	7 [1–12] *P*=0.02	4 [–2 to 10] *P*=0.18
Central PP, mm Hg	6 [1–12] *P*=0.03	–1 [–8 to 6] *P*=0.69	8 [0–16] *P*=0.045
Aortic stiffness			
cfPWV, m/s	0.66 [0.22–1.09] *P*=0.004	0.31 [–0.20 to 0.81] *P*=0.23	0.35 [–0.21 to 0.91] *P*=0.21
Steady arterial load			
SVR, dyne×s/cm^5	321 [150–492] *P*=0.0004	244 [44–443] *P*=0.02	78 [–143 to 299] *P*=0.48
Pulsatile arterial load			
Z_c, dyne×s/m^5	11.16 [–15.51 to 37.83] *P*=0.41	–17.01 [–48.13 to 14.11] *P*=0.28	28.17 [–6.27 to 62.61] *P*=0.11
PAC, ×10^{-6} cm^4/dyne	–1.48 [–3.40 to 0.43] *P*=0.13	0.41 [–1.81 to 2.64] *P*=0.71	–1.90 [–4.35 to 0.56] *P*=0.13
TAC, mL/mm Hg	–0.18 [–0.43 to 0.06] *P*=0.14	–0.01 [–0.29 to 0.28] *P*=0.96	–0.17 [–0.49 to 0.14] *P*=0.28
P_f, mm Hg	2.16 [–2.99 to 7.30] *P*=0.41	–4.65 [–10.65 to 1.35] *P*=0.13	6.81 [0.17–13.45] *P*=0.045
Peripheral wave reflections			
P_b, mm Hg	1.96 [0.15–3.78] *P*=0.03	0.65 [–1.46 to 2.76] *P*=0.54	1.32 [–1.02 to 3.66] *P*=0.27
AIx, %	5.34 [0.91–9.77] *P*=0.02	10.46 [5.29–15.63] *P*=0.0001	–5.12 [–10.84 to 0.60] *P*=0.08
Global reflection coefficient	0.02 [0.00–0.05] *P*=0.09	0.06 [0.03–0.09] *P*=0.0004	–0.03 [0.00–0.07] *P*=0.046

Models adjusted for age, time since last pregnancy, hypertension, serum creatinine, smoking history, and heart rate. AIx indicates augmentation index; aMD, adjusted mean difference; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; PAC, proximal aortic compliance; P_b, reflected pressure wave amplitude; PE-CO, preeclampsia with central obesity; PE-noCO, preeclampsia without central obesity; P_f, forward pressure wave amplitude; PP, pulse pressure; SVR, systemic vascular resistance; TAC, total arterial compliance; and Z_c, aortic characteristic impedance.

increase in the amplitude of the reflected waves in the PE-CO group.

To our knowledge, this is the first study to evaluate the combined effect of CO and preeclampsia on arterial hemodynamics. The prevalence of obesity is increasing and becoming one of the most frequent risk factors for adverse pregnancy outcomes, surpassing the reported prevalence of chronic hypertension.[31,32] The adverse cardiovascular health consequences of obesity are mediated in part by the presence of dysfunctional adipocytes in visceral adipose tissue.[33] These are responsible for insulin resistance, activation of the renin-angiotensin-aldosterone and neurohormonal systems, increased oxidative stress, endothelial dysfunction, and increased production of inflammatory cytokines. Similar mechanisms are thought to explain the higher risk of hypertensive disorders of pregnancy in women with obesity and the observed alterations of arterial health in the general population affected by obesity.[34] Moreover, the impact of preeclampsia on accelerated vascular aging is thought to be related to similar pathophysiological pathways, such as oxidative stress, inflammation, and endothelial dysfunction.[35] For example, increased serum levels of reactive oxygen species have been described both in women with previous preeclampsia and individuals with CO.[36,37] Yet, it is unclear whether the combination of these 2 key clinical factors leads to further worsening in oxidative stress and vascular aging.

Measures of central adiposity, such as WHR, better quantify the proportion of visceral adipose tissue than do noncentral adiposity measures such as body mass index.[11,38] The role and optimal measures of abdominal obesity preconception remain undetermined.[39] As opposed to waist circumference, the WHR has the advantage of indexing abdominal size to overall body size, and it has been suggested to better predict cardiovascular events in the general population.[40] In a systematic review by Heslehurst et al, the WHR was predictive of gestational diabetes, hypertensive disorders of pregnancy, and delivery-related outcomes.[39] Our results show that the WHR, a quick and noninvasive estimate of visceral adiposity, can also identify postpartum women with worse arterial health profiles,

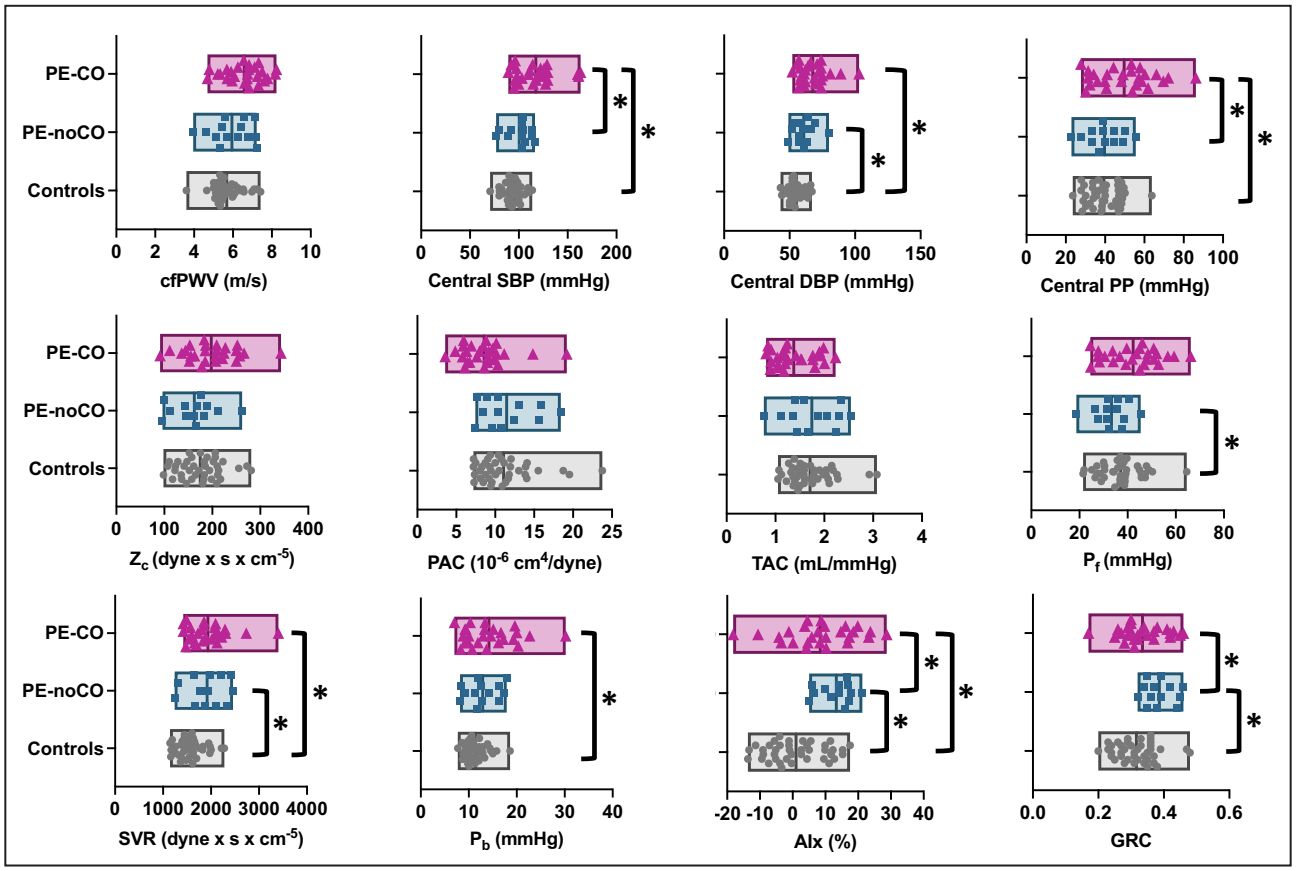


Figure 2. Comparison of arterial hemodynamics.
Scatterplot graphs of individual measures and floating boxes depicting distribution and mean value for each parameter of arterial hemodynamics in all 3 study groups. *P value <0.05 for adjusted pairwise comparison. AIx indicates augmentation index; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; GRC, global reflection coefficient; PAC, proximal aortic compliance; P_b, reflected pressure wave amplitude; PE-CO, preeclampsia with central obesity; PE-noCO, preeclampsia without central obesity; P_f, forward wave amplitude; PP, pulse pressure; SBP, systolic blood pressure; TAC, total arterial compliance; SVR, systemic vascular resistance; and Z_c, aortic characteristic impedance.

who would thus potentially be at higher risk of future cardiovascular events.

While a previous history of preeclampsia cannot be modified in a woman's life course, several strategies can be undertaken to improve cardiometabolic health and prognosis in individuals with CO, representing both a risk factor and a therapeutic target. In addition, some of these weight-management strategies have been shown to improve measures of arterial health. For example, Nordstrand et al showed a mean decline in cfPWV of 0.6 m/s (95% CI, 0.4–0.8 m/s) following a combined intensive lifestyle intervention of a 1000-kcal/day caloric restriction and supervised moderate to high intensity exercise training.[41] Similarly, in a meta-analysis of 1659 individuals (20 studies), an average 8% weight loss was associated with a reduction in pulse wave velocity of 0.32 m/s (95% CI, 0.24–0.41 m/s; I^2=26%). Ten of these studies had used an energy restriction diet while 8 studies combined calorie restrictive diet and exercise, without significant effect modification according to the intervention strategy.[42] Another study showed a decline in central BP after high-intensity resistance training for a duration of 12 weeks among young sedentary obese or overweight men.[43] These interventional strategies could be considered for evaluation and implementation of primary prevention programs targeting postpartum women affected by a preeclamptic pregnancy.

Strengths and Limitations

The main strength of our study is the extensive assessment of arterial hemodynamics in women with and without previous preeclampsia, allowing us to compare several domains of arterial health between groups. However, this study is not without limitations. The EVA study had a cross-sectional design, and inferences regarding causality and temporality of the associations we found cannot be made. Other obstetrical factors linked with cardiovascular risk, preeclampsia

and obesity, such as preterm birth and intrauterine growth restriction, could not be addressed in this analysis and deserve further attention to evaluate the specific contribution of each factor to arterial health. In addition, even though the EVA study is the largest investigation with extensive evaluation of arterial hemodynamics post preeclampsia, the sample size was relatively small and the results of these analyses should be interpreted as hypothesis-generating. Different hemodynamic domains appeared numerically worse in women with PE-CO and those with PE-noCO when compared with controls, but fewer domains were significantly different between the two groups with previous preeclampsia after model adjustment, which may be due to statistical power. Similarly, our sample size was not powered to perform statistical interaction testing between WHR and previous preeclampsia, which remains amenable to future studies with larger sample sizes. Last, invasive hemodynamic assessment would be considered the gold standard. However, it is fraught with potential risks. On the other hand, our noninvasive methods have been validated against catheter-based hemodynamic measurements and found to be accurate and reproducible, increasing potential clinical applicability.[44]

CONCLUSIONS

Women with a previous history of preeclampsia who present with CO 6 months to 6 years postpartum exhibit worse arterial health profiles as compared with age-matched controls without preeclampsia, with and without CO. Those with preeclampsia but without CO demonstrated substantially less hemodynamic alterations as compared with controls, limited to measures of wave reflection. Because arterial hemodynamic parameters have been shown to independently predict future cardiovascular events, our findings suggest that previously preeclamptic women who have CO may represent preferred candidates for targeted cardiovascular risk assessment and preventative measures.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology (A.P., T.C.) and Canadian Women's Heart Health Centre (A.P., T.C.), University of Ottawa Heart Institute, Ottawa, ON, Canada; Department of Obstetrics and Gynecology, The Ottawa Hospital, Ottawa, ON, Canada (A.W.); and Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (T.C.).

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Disclosures

None.

Supplemental Material

Data S1
Table S1
References 45,46

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